

**PCT**

**NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 08 September 2000 (08.09.00)	<b>Applicant's or agent's file reference</b> XA 3400
<b>International application No.</b> PCT/IB00/00165	<b>Priority date (day/month/year)</b> 05 January 1999 (05.01.99)
<b>International filing date (day/month/year)</b> 05 January 2000 (05.01.00)	
<b>Applicant</b> RIDET, Jean-Luc et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

20 July 2000 (20.07.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p align="center"><b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p align="center"><b>Authorized officer</b></p> <p align="center">Juan Cruz</p> <p>Telephone No.: (41-22) 338.83.38</p>
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# F. ENT COOPERATION TREA

**PCT**

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BOUVET, Philippe  
Aventis Pharma S. A.  
Patent Department  
20, avenue Raymond Aron  
F-92165 Antony  
FRANCE

<b>Date of mailing (day/month/year)</b> 08 September 2000 (08.09.00)	
<b>Applicant's or agent's file reference</b> XA 3400	<b>IMPORTANT NOTIFICATION</b>
<b>International application No.</b> PCT/IB00/00165	<b>International filing date (day/month/year)</b> 05 January 2000 (05.01.00)

1. The following indications appeared on record concerning: <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative		
<b>Name and Address</b> BOUVET, Philippe Rhone Poulenc Rorer S. A. Patent Department 20, avenue Raymond Aron F-92165 Antony France	<b>State of Nationality</b>	<b>State of Residence</b>
	<b>Telephone No.</b> 01 55 71 76 92	
	<b>Facsimile No.</b> 01 55 71 72 91	
	<b>Teleprinter No.</b>	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
<b>Name and Address</b> BOUVET, Philippe Aventis Pharma S. A. Patent Department 20, avenue Raymond Aron F-92165 Antony France	<b>State of Nationality</b>	<b>State of Residence</b>
	<b>Telephone No.</b> 01 55 71 76 92	
	<b>Facsimile No.</b> 01 55 71 72 91	
	<b>Teleprinter No.</b>	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: <div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> the receiving Office  <input type="checkbox"/> the International Searching Authority  <input checked="" type="checkbox"/> the International Preliminary Examining Authority                         </div> <div> <input type="checkbox"/> the designated Offices concerned  <input checked="" type="checkbox"/> the elected Offices concerned  <input type="checkbox"/> other:                         </div> </div>		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Juan Cruz  Telephone No.: (41-22) 338.83.38
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APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

Classification: A61K 48/00	A3	(11) International Publication Number: WO 00/40699
		(43) International Publication Date: 13 July 2000 (13.07.00)

Publication Number: PCT/IB00/00165  
Filing Date: 5 January 2000 (05.01.00)

Priority Date: 5 January 1999 (05.01.99) US

Designated States except US: AVENTIS  
[FR/FR]; Direction des brevets - Tri LEI  
Raymond Aron, F-92165 Antony (FR).

(for US only): RIDET, Jean-Luc  
Aron 77/514, CH-1010 Lausanne (CH).  
[FR/FR]; 18, rue Charcot, F-75013

Philippe; Aventis Pharma S.A., Patent  
Raymond Aron, F-92165 Antony

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(88) Date of publication of the international search report:  
2 November 2000 (02.11.00)

THEIR PREPARATION AND USES THEREOF

is an essentially pure preparation of human adult astrocytes, and a method of producing same. The purified treatment of neurodegenerative disorders or trauma to the central nervous system.

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LR	Liberia	SE	Sweden		
		SG	Singapore		

## INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/IB 00/00165

CT MATTER

C12N5/10

A61K48/00

Classification (IPC) or to both national classification and IPC

(classification system followed by classification symbols)

Minimum documentation to the extent that such documents are included in the fields searched

During the international search (name of data base and, where practical, search terms used)

CIS, WPI Data, PAJ, SCISEARCH, BIOTECHNOLOGY ABS, CHEM ABS Data,

## TO BE RELEVANT

, with indication, where appropriate, of the relevant passages

Relevant to claim No.

CORLINE J A ET AL:  
Isolation of human adult astrocyte  
derived from postmortem multiple  
sclerosis and control brain and spinal  
cords: Immunophenotypical and  
molecular characterization."  
JOURNAL OF NEUROSCIENCE RESEARCH,  
vol. 50, no. 3, August 1997 (1997-08),  
pages 334-354, XP000864697  
US  
5,800,401

1-6,  
13-18

column 1, paragraph 1 -column 2,  
column 1, paragraph 1 -page 348  
-/-

Indicated in the continuation of box C.



Patent family members are listed in annex.

Relevant prior art:

Relevant prior art of the art which is not  
relevant to the invention

Relevant prior art on or after the international

Publication of priority claim(s) or  
publication date of another  
document (as specified)

Disclosure, use, exhibition or

Relevant prior art international filing date but  
not claimed\*T\* later document published after the international filing date  
or priority date and not in conflict with the application but  
cited to understand the principle or theory underlying the  
invention\*X\* document of particular relevance; the claimed invention  
cannot be considered novel or cannot be considered to  
involve an inventive step when the document is taken alone\*Y\* document of particular relevance; the claimed invention  
cannot be considered to involve an inventive step when the  
document is combined with one or more other such docu-  
ments, such combination being obvious to a person skilled  
in the art.

\*A\* document member of the same patent family

Relevant prior art international search

Date of mailing of the international search report

26/07/2000

ISA

Office, P.O. Box 5818 Patentkan 2

Dallas, TX 75204, TX 75204, TX 75204, TX 75204,  
75204-3018

Authorized officer

De Kok, A

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## S CONSIDERED TO BE RELEVANT

nt, with indication, where appropriate, of the relevant passages

Relevant to claim No.

1135 A (UNIV NEW YORK)  
 ary 1994 (1994-01-20)

13,14,  
 17-19,  
 23,  
 25-27,  
 29-31

line 16 - line 26  
 line 33 -page 10, line 10  
 , line 27 -page 13, line 30

1,6

5631 A (UNIV CASE WESTERN RESERVE)  
 1991 (1991-05-16)  
 , line 21 -page 49, line 27

13,14

1,6

T AL.: "Human fetal astrocytes as  
 ivo gene therapy vehicle for  
 ing biologically active nerve  
 factor"

32

ENE THERAPY,

no. 3,  
 uary 1997 (1997-02-10), pages  
 , XP000864703

K US

le document

W ET AL.: "Gamma-interferon  
 s proliferation of adult human  
 tes in vitro and reactive gliosis  
 adult mouse brain in vivo"

13-18

INGS OF THE NATIONAL ACADEMY OF  
 S OF USA.,

, August 1991 (1991-08), pages  
 20, XP002142263

L ACADEMY OF SCIENCE. WASHINGTON.,

027-8424

n the application

16, column 2, paragraph 2

18; figure 2

1-6

IL ET AL: "Toward autologous ex  
 ne therapy for the central nervous  
 with human adult astrocytes"

1-32

ENE THERAPY,

, no. 2,  
 iary 1999 (1999-01-20), pages  
 ), XP002132470

043-0342

le document

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9401135	A	20-01-1994	AU	4664693 A	31-01-1994
WO 9106631	A	16-05-1991	US	5202120 A	13-04-1993
			AU	6918891 A	31-05-1991

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REC'D 11 APR 2001

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XA 3400	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB00/00165	International filing date (day/month/year) 05/01/2000	Priority date (day/month/year) 05/01/1999
International Patent Classification (IPC) or national classification and IPC C12N5/06		
Applicant AVENTIS PHARMA S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  20/07/2000	Date of completion of this report  06.04.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Wimmer, G  Telephone No. +49 89 2399 7347



INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

International application No. PCT/IB00/00165

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-33 as originally filed

**Claims, No.:**

1-32 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IB00/00165

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	11, 28
	No:	Claims	1-10, 12-27, 29-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**Re Item V**

**Reasoned statement under Art. 35(2) with regard to novelty, inventive step or industrial applicability.**

The application does not meet the requirements of Art. 33 PCT since claims 1-10, 12- 27 and 29-32 are not novel, and claims 11 and 28 do not appear to contain an inventive step.

- 1) Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

- D1: DE GROOT CORLINE J A ET AL: 'Establishment of human adult astrocyte cultures derived from postmortem multiple sclerosis and control brain and spinal cord regions: Immunophenotypical and functional characterization.' JOURNAL OF NEUROSCIENCE RESEARCH, vol. 49, no. 3, August 1997 (1997-08), pages 342-354, XP000864697 NEW YORK US ISSN: 0360-4012
- D2: WO 94 01135 A (UNIV NEW YORK) 20 January 1994 (1994-01-20)
- D4: LIN Q ET AL.: 'Human fetal astrocytes as an ex vivo gene therapy vehicle for delivering biologically active nerve growth factor' HUMAN GENE THERAPY, vol. 8, no. 3, 10 February 1997 (1997-02-10), pages 331-339, XP000864703 NEW YORK US

**Novelty under Art. 33(2) PCT.**

- 2) The method of claim 1 extends to the isolation or propagation of a population of astrocytes. Identical or similar methods have been disclosed repeatedly in the prior art. For instance, document D1 describes the isolation of astrocytes from adult human brain. The authors of D1 employ selective attachment of astrocytes to poly-L-lysine covered culture vessels, and removal of non-attached cells after 48 hours (page 344). This method leads to the recovery of a >95% pure astrocyte population as assessed by GFAP staining (page 347). Successive passages displayed even higher uniformity of population (>98%, page 347).

Therefore, claims 1-6, and claims 13-18 lack novelty.

- 3) Likewise, the procedures described in D4 include the isolation of human embryonic astrocytes by the method of McCarthy and de Vellis. This method, which is commonly known in the field, utilizes the differential attachment of astrocytes and other cell types, and allows to obtain populations of >98% purity (see McCarthy and de Vellis (1980), J. Cell Biol. 85(3), 890-2).  
The authors of D2 use thusly isolated human astrocytes for retrovirus-mediated transduction of murine  $\beta$ -NGF (Nerve Growth Factor) cDNA under the control of the MoMuLV LTR promoter.  
Accordingly, the method of D4 constitutes subject-matter of present claims 7-9, 12, 19-21, 24-27, 29-30 and 32 which consequently lack novelty.
- 4) Although adenoviral gene delivery as claimed in claim 10 was not performed by the authors of D4, the document describes that besides retroviral transfer, also gene transfer through adenoviruses is "likely to be applicable" (pg. 337). Claims 10 and 22 are therefore not considered as being novel.
- 5) While the method of D2 includes the essential features of claim 11 (isolation of rat astrocytes by adhesion and removal of nonadherent cells, subsequent introduction of external DNA through calcium phosphate precipitation), the method differs insofar as astrocytes are isolated after a 5 to 6 day attachment period rather than after two days. Claim 11 can therefore be regarded as being novel.
- 6) As a consequence of the product-by-process definition of claim 23, known subject-matter falls within the terms of the claim. For example, extrachromosomal DNA introduced by viruses is not distinguishable from the same DNA introduced by transfection. Similarly, integrated or native chromosomal DNA is not distinguishable from transfected and chromosomally recombined DNA. Claim 23 is therefore not novel.
- 7) The use of an astrocyte population as an implant according to claim 31 has been frequently described (see e.g. the application itself, desc. pg. 2; D2, pg. 2, l.22-pg. 3, l. 25, and references therein). Claim 31 therefore lacks novelty.

Inventive Step under Art. 33(3) PCT.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/IB00/00165

- 8) Novel claims 11 and 28 differ from the prior art in minor points only.  
The method of claim 11 is different to closest prior art, document D2, in the time of attachment of astrocytes only (see also sect. V.6). The IPEA does not see an unexpected result from the change from 5-6 days (D2) to 2 days of attachment. Furthermore, the skilled person would routinely investigate transfection (e.g. by calcium phosphate) of a human astrocyte culture as obtained through the method of D1, especially since D2 shows that rat astrocytes are transfectable by that method. Claim 11 therefore lacks an inventive step.
- 9) The use of DNA encoding an antisense-RNA, as referred to in claim 28, is a trivial alteration in a transfection method in general, and is not inventive.

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>XA 3400</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/IB 00/ 00165</b>	International filing date (day/month/year) <b>05/01/2000</b>	(Earliest) Priority Date (day/month/year) <b>05/01/1999</b>
Applicant <b>AVENTIS PHARMA S.A. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**ASTROCYTES, THEIR PREPARATION AND USES THEREOF**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

IB 00/00165

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N5/06 C12N5/10 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, SCISEARCH, BIOTECHNOLOGY ABS, CHEM ABS Data, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DE GROOT CORLINE J A ET AL:  "Establishment of human adult astrocyte cultures derived from postmortem multiple sclerosis and control brain and spinal cord regions: Immunophenotypical and functional characterization."  JOURNAL OF NEUROSCIENCE RESEARCH,  vol. 49, no. 3, August 1997 (1997-08),  pages 342-354, XP000864697  NEW YORK US  ISSN: 0360-4012  abstract  page 344, column 1, paragraph 1 -column 2,  paragraph 2  page 347, column 1, paragraph 1 -page 348  ---  -/--</p>	1-6, 13-18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

11 July 2000

Date of mailing of the international search report

26/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/00165

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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